

We claim:

1. A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to said animal a therapeutically effective amount of a composition comprising [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) or a physiologically functional derivative thereof, and (2*R*, 5*S*, *cis*)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (emtricitabine) or a physiologically functional derivative thereof.

10 2. The method according to claim 1 wherein the composition comprises tenofovir disoproxil fumarate and emtricitabine.

3. The method according to claim 2 wherein the composition comprises about 300 mg of tenofovir disoproxil fumarate and about 200 mg of emtricitabine.

15 4. The method according to claim 1 wherein tenofovir disoproxil fumarate or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of about 1:50 to about 50:1 by weight.

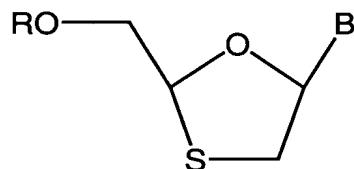
20 5. The method according to claim 1 wherein tenofovir disoproxil fumarate or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of about 1:10 to about 10:1 by weight.

25 6. The method according to claim 1 wherein tenofovir disoproxil fumarate or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are each present in an amount from about 1 mg to about 1000 mg per unit dosage form.

7. The method according to claim 1 wherein tenofovir disoproxil fumarate or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are each present in an amount from about 100 mg to about 300 mg per unit dosage form.

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8. A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to said animal a therapeutically effective amount of a composition comprising [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate
10 (tenofovir disoproxil fumarate) or a physiologically functional derivative thereof, and a compound of the formula:



wherein B is selected from adenine, guanine, cytosine, uracil, thymine, 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, 15 nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-fluorocytosine, 5-chlorocytosine, 5-bromocytosine, 5-iodocytosine, pseudouridine, pseudouridylcytosine, 5-propynylcytosine, 20 isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6 -methylguanine, N^6 -methyladenine, O^4 -methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, and a pyrazolo[3,4-D]pyrimidine; and

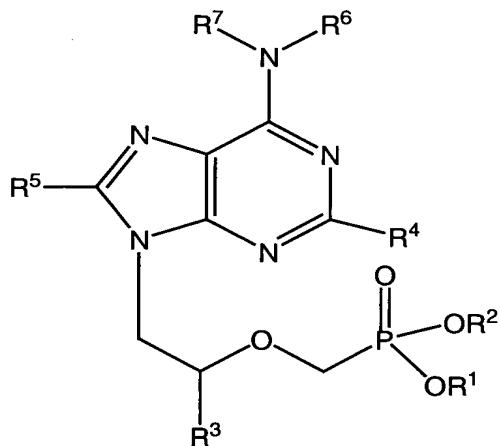
R is selected from H, C₁–C₁₈ alkyl, C₁–C₁₈ substituted alkyl, C₂–C₁₈ alkenyl, C₂–C₁₈ substituted alkenyl, C₂–C₁₈ alkynyl, C₂–C₁₈ substituted alkynyl, C₆–C₂₀ aryl, 25 C₆–C₂₀ substituted aryl, C₂–C₂₀ heterocycle, C₂–C₂₀ substituted heterocycle, phosphonate, phosphophosphonate, diphosphophosphonate, phosphate, diphosphate, triphosphate, polyethyleneoxy, and a prodrug moiety.

9. The method according to claim 1 wherein one component of composition is (2*R*, 5*S*, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (3TC).

5 10. The method according to claim 1 wherein the composition comprises a physiologically functional derivative of emtricitabine which is a racemic mixture of the enantiomers (2*R*, 5*S*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one and (2*S*, 5*R*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one.

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11. The method according to claim 1 wherein the composition comprises a physiologically functional derivative of tenofovir disoproxil fumarate which has the structure:



15 wherein R¹ and R² are independently selected from H, C₁–C₆ alkyl, C₁–C₆ substituted alkyl, C₆–C₂₀ aryl, C₆–C₂₀ substituted aryl, C₆–C₂₀ arylalkyl, C₆–C₂₀ substituted arylalkyl, acyloxymethyl esters –CH₂OC(=O)R and acyloxymethyl carbonates –CH₂OC(=O)OR⁹ where R⁹ is C₁–C₆ alkyl, C₁–C₆ substituted alkyl, C₆–C₂₀ aryl and C₆–C₂₀ substituted aryl;

20 R³ is selected from H, C₁–C₆ alkyl, C₁–C₆ substituted alkyl, or CH₂OR⁸ where R⁸ is C₁–C₆ alkyl, C₁–C₆ hydroxyalkyl and C₁–C₆ haloalkyl;

R⁴ and R⁵ are independently selected from H, NH₂, NHR and NR₂ where R is C₁-C₆ alkyl; and

R⁶ and R⁷ are independently selected from H and C₁-C₆ alkyl;
or a pharmaceutically acceptable salt or solvate thereof.

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12. The method according to claim 11 wherein at least one of R₁ and R₂ is
-CH₂OC(=O)C(CH₃)₃.

13. The method according to claim 11 wherein at least one of R₁ and R₂ is
10 -CH₂OC(=O)OC(CH₃)₃.

14. The method according to claim 11 wherein at least one of R₁ and R₂ is
-CH₂OC(=O)OCH(CH₃)₂.

15. A method for the treatment or prevention of the symptoms or effects of an
HIV infection in an infected animal comprising administering in combination or
alternation a therapeutically effective amount of [2-(6-amino-purin-9-yl)-1-methyl-
ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate
(tenofovir disoproxil fumarate) or a physiologically functional derivative thereof, and
20 (2R, 5S, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-
pyrimidin-2-one (emtricitabine) or a physiologically functional derivative thereof.

16. The method according to claim 15 wherein tenofovir disoproxil fumarate
or a physiologically functional derivative thereof, and emtricitabine or a physiologically
25 functional derivative thereof, are administered in alternation.

17. The method according to claim 15 wherein tenofovir disoproxil fumarate
or a physiologically functional derivative thereof, and emtricitabine or a physiologically

functional derivative thereof, are administered in combination as a single combined formulation.

18. The method according to claim 17 wherein the single combined
5 formulation is administered once per day to an infected human.

19. The method according to claim 1 in which said animal is a human.

20. The method according to claim 1 wherein the composition further
10 comprises a third active ingredient selected from a protease inhibitor (PI), a nucleoside reverse transcriptase inhibitor (NRTI), a non- nucleoside reverse transcriptase inhibitor (NNRTI), and an integrase inhibitor.

21. The method according to claim 20 wherein the third active ingredient is 9-
15 [R-2-[[[S]-[[[S]-1-(isopropoxycarbonyl)ethyl]amino]-phenoxyphosphinyl]methoxy]propyl]adenine (GS-7340).

22. The method according to claim 1 wherein the composition further
comprises a pharmaceutically acceptable glidant.

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23. The method according to claim 22 wherein the glidant is selected from silicon dioxide, powdered cellulose, microcrystalline cellulose, metallic stearates, sodium aluminosilicate, sodium benzoate, calcium carbonate, calcium silicate, corn starch, magnesium carbonate, asbestos free talc, stearowet C, starch, starch 1500,
25 magnesium lauryl sulfate, magnesium oxide, and combinations thereof.

24. The method according to claim 23 wherein the metallic stearates are selected from calcium stearate, magnesium stearate, zinc stearate, and combinations thereof.

5 25. A pharmaceutical formulation comprising [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) or a physiologically functional derivative thereof and (2R, 5S, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine) or a physiologically functional derivative thereof.

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26. The pharmaceutical formulation according to claim 25 further comprising one or more pharmaceutically acceptable carriers or excipients.

15 27. The pharmaceutical formulation according to claim 26 wherein the pharmaceutically acceptable carriers or excipients are selected from pregelatinized starch, croscarmellose sodium, povidone, lactose monohydrate, microcrystalline cellulose, and magnesium stearate; and combinations thereof.

20 28. The pharmaceutical formulation according to claim 25 wherein tenofovir disoproxil fumarate or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of 1:50 to 50:1 by weight.

25 29. The pharmaceutical formulation according to claim 25 wherein tenofovir or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are present in a ratio of 1:10 to 10:1 by weight.

30. The pharmaceutical formulation according to claim 25 in unit dosage form.

31. The pharmaceutical formulation according to claim 30 wherein tenofovir disoproxil fumarate or a physiologically functional derivative thereof and emtricitabine or a physiologically functional derivative thereof are each and individually present in an amount from 100 mg to 1000 mg per unit dosage form.

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32. The pharmaceutical formulation according to claim 31 comprising tenofovir disoproxil fumarate and emtricitabine.

33. The pharmaceutical formulation according to claim 32 comprising about
10 300 mg of tenofovir disoproxil fumarate and about 200 mg of emtricitabine.

34. The pharmaceutical formulation according to claim 25 suitable for oral administration.

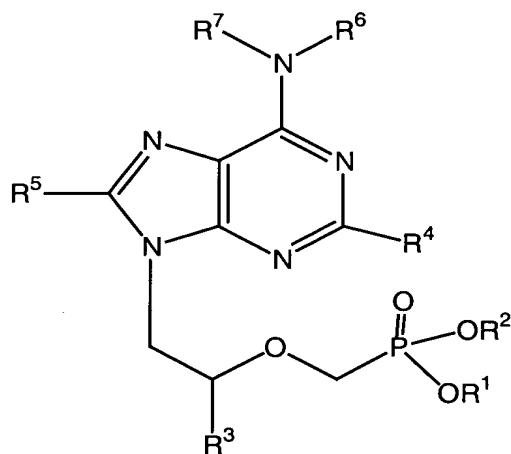
15 35. The pharmaceutical formulation according to claim 25 in the form of a tablet or capsule.

36. The pharmaceutical formulation according to claim 25 suitable for administration once per day to an infected human.

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37. The pharmaceutical formulation according to claim 25 comprising a physiologically functional derivative of emtricitabine which is (*2R, 5S, cis*)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (3TC).

25 38. The pharmaceutical formulation according to claim 25 wherein the combination comprises a physiologically functional derivative of tenofovir disoproxil fumarate which has the structure:



wherein R¹ and R² are independently selected from H, C₁–C₆ alkyl, C₁–C₆ substituted alkyl, C₆–C₂₀ aryl, C₆–C₂₀ substituted aryl, C₆–C₂₀ arylalkyl, C₆–C₂₀ substituted arylalkyl, acyloxymethyl esters –CH₂OC(=O)R and acyloxymethyl carbonates –CH₂OC(=O)OR⁹ where R⁹ is C₁–C₆ alkyl, C₁–C₆ substituted alkyl, C₆–C₂₀ aryl or C₆–C₂₀ substituted aryl;

R³ is H, C₁–C₆ alkyl, C₁–C₆ substituted alkyl, or CH₂OR⁸ where R⁸ is C₁–C₆ alkyl, C₁–C₆ hydroxyalkyl or C₁–C₆ haloalkyl;

R⁴ and R⁵ are independently selected from H, NH₂, NHR and NR₂ where R is C₁–C₆ alkyl; and

R⁶ and R⁷ are independently selected from H and C₁–C₆ alkyl; or a pharmaceutically acceptable salt or solvate thereof.

39. The pharmaceutical formulation according to claim 38 wherein at least one of R¹ and R² is –CH₂OC(=O)C(CH₃)₃.

40. The pharmaceutical formulation according to claim 38 wherein at least one of R¹ and R² is –CH₂OC(=O)OC(CH₃)₃.

41. The pharmaceutical formulation according to claim 38 wherein at least one of R¹ and R² is –CH₂OC(=O)OCH(CH₃)₂.

42. A patient pack comprising at least one active ingredient selected from [2-(6-amino-purin-9-yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester fumarate (tenofovir disoproxil fumarate) and (2*R*, 5*S*, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one (emtricitabine), and an information insert containing directions on the use of tenofovir and emtricitabine together in combination.

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10 43. The patient pack according to claim 42 comprising a co-formulated pill, tablet, caplet, or capsule of 100 to 1000 mg of tenofovir disoproxil fumarate and 100 to 1000 mg of emtricitabine.

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44. The patient pack according to claim 43 comprising a co-formulated pill, tablet, caplet, or capsule of 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine.

45. The patient pack according to claim 42 comprising a separate pill, tablet, caplet, or capsule of 100 to 1000 mg of tenofovir disoproxil fumarate and 100 to 1000 mg of emtricitabine.

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46. The patient pack according to claim 45 comprising a separate pill, tablet, caplet, or capsule of 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine.

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47. A chemically stable combination of tenofovir disoproxil fumarate and emtricitabine.

48. The chemically stable combination of Claim 47 wherein the combination is a pharmaceutical dosage form.

49. The chemically stable combination of Claim 48 wherein the dosage form
is oral.

50. The chemically stable combination of any of Claims 47, 48, or 49 which
5 further comprises a third antiviral agent.

51. The chemically stable combination of Claim 50 where in the third
antiviral agent is an NNRTI or PI.

10 52. The chemically stable combination of Claim 51 wherein the third antiviral
agent is a PI.

53. The chemically stable combination of Clam 51 wherein the third antiviral
agent is an NNRTI.

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54. The chemically stable combination of Claim 50 wherein the third antiviral
agent is selected from Reyataz, Kaletra or Sustiva.

20 55. A chemically stable oral pharmaceutical dosage form comprising
tenofovir disoproxil fumarate and emtricitabine.

56. A chemically stable oral pharmaceutical dosage form comprising
tenofovir disoproxil fumarate, emtricitabine and Reyataz.

25 57. A chemically stable oral pharmaceutical dosage form comprising
tenofovir disoproxil fumarate, emtricitabine and Kaletra.

58. A chemically stable oral pharmaceutical dosage form comprising tenofovir disoproxil fumarate, emtricitabine and Sustiva.